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Influx of Fentanyl-laced Counterfeit Pills and Toxic Fentanyl-related Compounds Further Increases Risk of Fentanyl-related Overdose and Fatalities

Summary

On October 26, 2015, CDC issued HAN 384 (<http://emergency.cdc.gov/han/han00384.asp>) that alerted (1) public health departments, health care professionals, first responders, and medical examiners and coroners of the increase in fentanyl-related unintentional overdose fatalities in multiple states primarily driven by illicitly manufactured fentanyl (IMF) (i.e., non-pharmaceutical fentanyl); (2) provided recommendations for improving detection of fentanyl-related overdose outbreaks; and (3) encouraged states to expand access to naloxone and training for administering naloxone to reduce opioid overdose deaths.

The purpose of this HAN update is to alert public health departments, health care professionals, first responders, and medical examiners and coroners to new developments that have placed more people at risk for fentanyl-involved overdoses from IMF and may increase the risk of non-fatal and fatal overdose. These developments include the following: (1) a sharp increase in the availability of counterfeit pills containing varying amounts of fentanyl and fentanyl-related compounds (e.g., labeled as Oxycodone, Xanax, and Norco), (2) the potential for counterfeit pills containing fentanyl and fentanyl-related compounds to be broadly distributed across the United States which could impact states not previously impacted by IMF and persons using diverted prescription pills (i.e., licit drugs diverted for illicit purposes and involves the diversion of drugs from legal and medically necessary uses towards uses that are illegal and typically not medically authorized or necessary)[1], (3) the widening array of toxic fentanyl-related compounds being mixed with heroin or sold as heroin, including extremely toxic analogs such as carfentanil, and (4) continued increases in the supply and distribution of IMF (<http://www.cdc.gov/drugoverdose/data/fentanyl-le-reports.html>).

Background

In July 2016, the Drug Enforcement Administration (DEA) issued a nationwide report indicating that hundreds of thousands of counterfeit pills have been entering the U.S. drug market since 2014, some containing deadly amounts of fentanyl and fentanyl analogs [2]. Traditionally, fentanyl and fentanyl analogs in the illicit market have been mixed into heroin or sold as heroin, often without the knowledge of the consumer, and have primarily impacted areas where white powder heroin is prevalent, including the Northeast, Midwest, and Southeast regions of the United States. The influx of counterfeit pills, which closely resemble oxycodone [2,3], Xanax [3], and Norco [4,5], has increased the chance of fentanyl-involved overdoses among persons misusing prescription opioids or benzodiazepines who seek diverted medications on the illicit market [2], in addition to persons who inject, sniff, or snort drugs. Persons who misuse prescription pills are geographically widespread; thus, the potential risk for fentanyl overdose has spread beyond those regions previously known to be impacted by IMF, and could intensify the impact in regions already affected by IMF.

The supply, distribution, and potency of illicitly manufactured fentanyl and fentanyl-related compounds in the U.S. drug market is evolving. Carfentanil, an extremely potent fentanyl analog, has been detected in at least one state [6,7] and is currently being investigated as a possibility in a few other locations [8]. Designed in 1974, carfentanil was previously used exclusively for veterinary use with large animals and is not approved for use in humans, as it has been shown to be 100 times more potent than fentanyl in animal studies. Other fentanyl-related compounds have been reported by the DEA National Forensic Laboratory Information System (NFLIS), which systematically collects drug identification results from drug

cases submitted for analysis to forensic laboratories (referred to as drug submissions). From 2014 to 2015 the number of drug submissions testing positive for acetyl fentanyl increased substantially, rising from 463 in 2014 to 1,870 in 2015[9,10,11], and in 2016, NFLIS reported increasing drug submissions testing positive for fentanyl (244 drug submissions from January to July 2016) [9]. States should be vigilant about the possibility of highly toxic fentanyl-related compounds becoming available in the illicit drug market, as well as other highly toxic synthetic opioid derivatives, such as U47700 [2,12].

NFLIS has reported that the overall supply of illicitly manufactured fentanyl appears to have substantially increased from 2014 to 2015, with the number of drug submissions testing positive for illicitly manufactured fentanyl doubling during this period (from 5,343 to 13,882). The number of states reporting more than 100 fentanyl submissions also increased during this period from 11 to 15 (<http://www.cdc.gov/drugoverdose/data/fentanyl-le-reports.html> [9]). Recently, according to NFLIS and National Seizure System (NSS) reports, the amount of fentanyl seized in the United States has nearly doubled; from October 2014 to September 2015, federal, state, and local law enforcement agencies seized a total of 167.7 kilograms of fentanyl, and through June, 2016, they seized 363.8 kilograms of fentanyl [9].

Recommendations

CDC suggests the following actions in response to the increased risk of fentanyl overdose from IMF due to the influx of fentanyl-laced counterfeit pills, the widening array of highly toxic fentanyl-related compounds, and the continued expansion and geographic spread of the IMF supply:

(1) Improve detection of fentanyl outbreaks to facilitate effective response.

- *Public health departments:*
 - Explore methods for rapidly identifying drug overdose outbreaks through use of existing surveillance systems such as medical examiner data, emergency medical services data, near-real time emergency department data, and poison center data [13].
 - Consider engaging local poison centers to assist with treatment of patients (toll free phone number is 800- 222-1222).
 - Track and monitor geographic trends in fentanyl and heroin supply using DEA's National Forensic Laboratory Information System (NFLIS) reports (see NFLIS Report http://www.deadiversion.usdoj.gov/nflis/spec_rpt_opioids_2014.pdf). National Heroin Threat Assessment Summaries (see NHTA Summary https://www.dea.gov/divisions/hq/2016/hq062716_attach.pdf) and alerts on the DEA website [2] to inform prevention and response efforts.
 - Raise awareness among key partners and stakeholders to the widening profile of those at risk for fentanyl overdose, which increasingly includes persons misusing diverted prescribed oral pain and sedative medications [2].
 - Track decedent demographics and known risk factors (e.g., drug type, recent release from an institution, previous overdose) to inform prevention efforts [14].
 - Develop general public health messaging about fentanyl, including fentanyl-laced counterfeit pills and fentanyl-related compounds that emphasizes the toxicity and potential lethality of the drug versus its high "potency." The messaging should include warnings of the highly variable content of fentanyl present in illicit products, which further elevates risk of overdose [12,15].
- *Medical examiners and coroners:*
 - Screen for fentanyl in suspected opioid overdose cases in regions reporting increases in fentanyl seizures, fentanyl-related overdose fatalities, or unusually high spikes in heroin or unspecified drug overdose fatalities.
 - Screen specimens using an ELISA test that can detect fentanyl. Confirmatory gas chromatography mass spectrometry (GC-MS) of positive screens for fentanyl may either confirm the presence of fentanyl or suggest the presence of a fentanyl analog. [16]. When fentanyl screening is negative, or confirmatory testing is inconclusive, yet opioid or fentanyl overdose is highly suspected, consider specialized testing for fentanyl analogs, particularly if an increase in overdoses is occurring.

- *Law Enforcement:* Law enforcement plays an important role in identifying and responding to increases in the distribution and use of illicitly manufactured fentanyl.
 - Use extreme caution when handling suspected illicitly manufactured fentanyl, white powders, and unknown substances (see DEA warning <https://www.dea.gov/divisions/hq/2016/hq061016.shtml>). Use appropriate safety precautions and personal protective equipment (see NIOSH Emergency Response Card http://www.cdc.gov/niosh/ershdb/emergencyresponsecard_29750022.html).
 - Prioritize and expedite laboratory testing of drug samples taken from drug overdose scenes, if possible.
 - Share data on fentanyl and fentanyl analog drug seizures with local health departments, medical examiners, and coroners.
 - Carry a supply of naloxone so that it can be administered immediately to mitigate the effects of the overdose. (See Recommendation 2 below.)
- *Laboratories:* The following government forensic laboratories supporting law enforcement can provide assistance with reference materials or reference data on a case-by-case basis.
 - DEA Reference Materials Program- DEALabRefMaterials@usdoj.gov
 - DEA Emerging Trends Program- DEA.Emerging.Trends@usdoj.gov
 - Scientific Working Group for the Analysis of Seized Drugs - [SWGDRUG.ORG](http://www.swgdrugs.org)

(2) Expand Use of Naloxone and Treatment

- *Health Care Providers:*
 - Multiple dosages of naloxone may need to be administered per overdose event, because of fentanyl's increased potency relative to other opioids. Orally-ingested counterfeit pills laced with fentanyl may require prolonged dosing of naloxone in the ED/hospital setting due to a delayed toxicity that has been reported in some cases [15].
 - Facilitate access to Medication-Assisted Treatment (MAT). MAT is a comprehensive approach to addressing the needs of persons with opioid use disorders that combines the use of medication with counseling and behavioral therapies. Providers should discuss treatment options with persons who have an opioid use disorder, and persons who have experienced an opioid-related overdose once they are stabilized.
- *Harm reduction organizations:*
 - Expand naloxone access to persons at risk for opioid-related overdose and to their friends and family members [17].
 - Train those using drugs how to effectively administer naloxone and emphasize the importance of calling 911 immediately after recognition of an overdose, because naloxone that is available in the field may be insufficient to reverse the overdose.

For more information

- CDC Health Advisory: Recommendations for Laboratory Testing for Acetyl Fentanyl and Patient Evaluation and Treatment for Overdose with Synthetic Opioid at <http://emergency.cdc.gov/han/han00350.asp>
- Canadian Centre on Substance Abuse Bulletin: Novel Synthetic Opioids in Counterfeit Pharmaceuticals and Other Illicit Street Drugs at (see CCENDU Bulletin <http://www.ccsa.ca/Resource%20Library/CCSA-CCENDU-Novel-Synthetic-Opioids-Bulletin-2016-en.pdf>).
- MMWR: Fentanyl Law Enforcement Submissions and Increases in Synthetic Opioid–Involved Overdose Deaths — 27 States, 2013–2014 http://www.cdc.gov/mmwr/volumes/65/wr/mm6533a2.htm?s_cid=mm6533a2_w
- MMWR: Increase in Fentanyl-Related Overdose Deaths — Ohio and Florida, 2010–2015 http://www.cdc.gov/mmwr/volumes/65/wr/mm6533a3.htm?s_cid=mm6533a3_w
- SAMHSA Opioid Overdose Toolkit at: http://store.samhsa.gov/shin/content/SMA13-4742/Overdose_Toolkit_2014_Jan.pdf

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